REMARKS

Added claims 56-63 are fully supported throughout the specification of the captioned application, and by the original claims. Entry of the foregoing amendments prior to examination is respectfully requested.

Respectfully submitted,

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Date

Paul M. Booth
Reg. No. 40,244

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5300
Facsimile: (202)672-5399

Claims

1. A method of setting up one or more nucleic acid sequences encoding one or more (poly)peptide sequences suitable for the creation of libraries of (poly)peptides said (poly)peptide sequences comprising amino acid consensus sequences, said method comprising the following steps:
   (a) deducing from a collection of at least three homologous proteins one or more (poly)peptide sequences comprising at least one amino acid consensus sequence;
   (b) optionally, identifying amino acids in said (poly)peptide sequences to be modified so as to remove unfavorable interactions between amino acids within or between said or other (poly)peptide sequences;
   (c) identifying at least one structural sub-element within each of said (poly)peptide sequences;
   (d) backtranslating each of said (poly)peptide sequences into a corresponding coding nucleic acid sequence;
   (e) setting up cleavage sites in regions adjacent to or between the ends of sub-sequences encoding said sub-elements, each of said cleavage sites:
      (ea) being unique within each of said coding nucleic acid sequences;
      (eb) being common to the corresponding sub-sequences of any said coding nucleic acids.

2. A method of setting up two or more sets of one or more nucleic acid sequences comprising executing the steps described in claim 1 for each of said sets with the additional provision that said cleavage sites are unique between said sets.

3. The method of claim 2 in which at least two of said sets are deduced from the same collection of at least three homologous proteins.

4. The method according to any one of claims 1 to 3, wherein said setting up further comprises the synthesis of said nucleic acid coding sequences.

5. The method according to any one of claims 1 to 4, further comprising the cloning of said nucleic acid coding sequences into a vector.

6. The method according to any one of claims 1 to 5, wherein said removal of unfavorable interactions results in enhanced expression of said (poly)peptides.

7. The method according to any one of claims 1 to 6, further comprising the steps of:
   (f) cleaving at least two of said cleavage sites located in regions adjacent to or between the ends of said sub-sequences; and
   (g) exchanging said sub-sequences by different sequences; and
   (h) optionally, repeating steps (f) and (g) one or more times.

8. The method according to claim 7, wherein said different sequences are selected from the group of different sub-sequences encoding the same or different sub-elements derived from the same or different (poly)peptides.

9. The method according to claims 7 or 8, wherein said different sequences are selected from the group of:
   (i) genomic sequences or sequences derived from genomic sequences;
   (ii) rearranged genomic sequences or sequences derived from rearranged genomic sequences; and
   (iii) random sequences.

10. The method according to any one of claims 1 to 9 further comprising the expression of said nucleic acid coding sequences.

11. The method according to any one of claims 1 to 10 further comprising the steps of:
   (i) screening, after expression, the resultant (poly)peptides for a desired property;
   (k) optionally, repeating steps (f) to (i) one or more times with nucleic acid sequences encoding one or more (poly)peptides obtained in step (i).

12. The method according to claim 11, wherein said desired property is selected from the group of optimized affinity or specificity for a target molecule, optimized enzymatic activity, optimized expression yields, optimized stability and optimized solubility.

13. The method according to any one of claims 1 to 12, wherein said cleavage sites are sites cleaved by restriction enzymes.

14. The method according to any one of claims 1 to 13, wherein said structural sub-elements comprise between 1 and 150 amino acids.

15. The method according to claim 14, wherein said structural sub-elements comprise between 3 and 25 amino acids.

16. The method according to any one of claims 1 to 15, wherein said nucleic acid is DNA.

17. The method according to any one of claims 1 to 16, wherein said (poly)peptides have an amino acid pattern characteristic of a particular species.

18. The method according to claim 17, wherein said species is human.

19. The method according to any one of claims 1 to 18, wherein said (poly)peptides are at least part of members or derivatives of the immunoglobulin superfamily.

20. The method according to claim 19, wherein said members or derivatives of the immunoglobulin superfamily are members or derivatives of the immunoglobulin family.

21. The method according to claim 19 or 20, wherein said (poly)peptides are or are derived from heavy or light chain variable regions wherein said structural sub-elements are framework regions (FR) 1, 2, 3, or 4 or complementary determining regions (CDR) 1, 2, or 3.

22. The method according to claim 20 or 21, wherein said (poly)peptides are or are derived from the HuCAL consensus genes:
Vκ1, Vκ2, Vκ3, Vκ4, Vλ1, Vλ2, Vλ3, VH1A, VH1B, VH2, VH3, VH4, VH5, VH6, Cκ, Cλ, CH1 or any combination of said HuCAL consensus genes.

23. The method according to any one of claims 20 to 22, wherein said derivative of said immunoglobulin family or said combination is an Fv, disulphide-linked Fv, single-chain Fv (scFv), or Fab fragment.

24. The method according to claims 22 to 23, wherein said derivative is an scFv fragment comprising the combination of HuCAL VH3 and HuCAL Vλ2 consensus genes that comprises a random sub-sequence encoding the heavy chain CDR3 sub-element.

25. The method according to any one of claims 1 to 24, wherein at least part of said (poly)peptide sequences or (poly)peptides is connected to a sequence encoding at least one additional moiety or to at least one additional moiety, respectively.

26. The method according to claim 25, wherein said connection is formed via a contiguous nucleic acid sequence or amino acid sequence, respectively.

27. The method according to claims 25 to 26, wherein said additional moiety is a toxin, a cytokine, a reporter enzyme, a moiety being capable of binding a metal ion, a peptide, a tag suitable for detection and/or purification, or a homo- or hetero-association domain.

28. The method according to any one of claims 10 to 27, wherein the expression of said nucleic acid sequences results in the generation of a repertoire of biological activities and/or specificities, preferably in the generation of a repertoire based on a universal framework.

29. A nucleic acid sequence obtainable by the method according to any of claims 1 to 28.

30. A collection of nucleic acid sequences obtainable by the method according to any of claims 1 to 28.

31. A recombinant vector obtainable by the method according to any of claims 5 to 28.

32. A collection of recombinant vectors obtainable by the method according to any of claims 5 to 30.

33. A host cell transformed with the recombinant vector according to claim 31.

34. A collection of host cells transformed with the collection of recombinant vectors according to claim 32.

35. A method of producing a (poly)peptide or a collection of (poly)peptides as defined in any of claims 1 to 28 comprising culturing the host cell according to claim 33 or the collection of host cells according to claim 34 under suitable conditions and isolating said (poly)peptide or said collection of (poly)peptides.

36. A (poly)peptide devisable by the method according to any one of claims 1 to 3, encoded by the nucleic acid sequence according to claim 29 or obtainable by the method according to any one of claims 4 to 28 or 35.

37. A collection of (poly)peptides devisable by the method according to any one of claims 1 to 3, encoded by the collection of nucleic acid sequences according to claim 30 or obtainable by the method according to any one of claims 4 to 28 or 35.

38. A vector suitable for use in the method according to any of claims 5 to 28 and 35 characterized in that said vector is essentially devoid of any cleavage site as defined in claim 1(e) and 2.

39. The vector according to claim 38 which is an expression vector.

40. A kit comprising at least one of:
(a) a nucleic acid sequence according to claim 29;
(b) a collection of nucleic acid sequences according to claim 30;
(c) a recombinant vector according to claim 31;
(d) a collection of recombinant vectors according to claim 32;
(e) a (poly)peptide according to claim 36;
(f) a collection of (poly)peptides according to claim 37;
(g) a vector according to claim 38 or 39; and optionally,
(h) a suitable host cell for carrying out the method according to claim 35.

41. A method of designing two or more genes encoding a collection of two or more proteins, comprising the steps of:

(a) either

(aa) identifying two or more homologous gene sequences, or

(ab) analyzing at least three homologous genes, and

deducing two or more consensus gene sequences therefrom,

(b) optionally, modifying codons in said consensus gene sequences to remove unfavourable interactions between amino acids in the resulting proteins,

(c) identifying sub-sequences which encode structural sub-elements in said consensus gene sequences

(d) modifying one or more bases in regions adjacent to or between the ends of said sub-sequences to define one or more cleavage sites, each of which:

(da) are unique within each consensus gene sequence,

(db) do not form compatible sites with respect to any single sub-sequence,

(dc) are common to all homologous sub-sequences.

42. A method of preparing two or more genes encoding a collection of two or more proteins, comprising the steps of :

(a) designing said genes according to claim 41, and

(b) synthesizing said genes.

43. A collection of genes prepared according to the method of claim 42.

44. A collection of two or more genes derived from gene sequences which:

(a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

(b) carry cleavage sites, each of which:

(ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,

(bb) are unique within each gene sequence,

(bc) do not form compatible sites with respect to any single sub-sequence, and

(bd) are common to all homologous sub-sequences.

45. The collection of genes according to either of claims 43 or 44 in which each of said gene sequences has a nucleotide composition characteristic of a particular species.

46. The collection of genes according to claim 45 in which said species is human.

47. The collection of genes according to any of claims 43 to 46 in which one or more of said gene sequences encodes at least part of a member of the immunoglobulin superfamily, preferably of the immunoglobulin family.

48. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody heavy chains.

49. The collection of genes according to claim 47 in which said structural sub-elements correspond to any combination of framework regions 1, 2, 3, and 4, and/or CDR regions 1, 2, and 3 of antibody light chains.

50. A collection of vectors comprising a collection of gene sequences according to any of claims 43 to 49.

51. The collection of vectors according to claim 50 comprising the additional feature that the vector does not comprise any cleavage site that is contained in the collection of genes according to any of claims 43 to 49.

52. A method for identifying one or more genes encoding one or more proteins having a desirable property, comprising the steps of:

(a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins.

(b) screening said collection to isolate one or more proteins having a desired property,

(c) identifying the genes encoding the proteins isolated in step (b),

(d) optionally, excising from the genes encoding the proteins isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or more second sub-sequences encoding structural sub-elements, to generate new vectors according to either of claims 50 or 51,

(e) optionally, repeating steps (a) to (c).

53. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of:

(a) expressing from the collection of vectors according to either of claims 50 or 51 a collection of proteins,

(b) screening said collection to isolate one or more antibody fragments which bind to said target,

(c) identifying the genes encoding the proteins isolated in step (b),

(d) optionally, excising from the genes encoding the antibody fragments isolated in step (b) one or more genetic sub-sequences encoding structural sub-elements, and replacing said sub-sequence(s) by one or

more second sub-sequences encoding structural sub-generate new vectors according to either of claims 50 or 51,

(e) optionally, repeating steps (a) to (c).

54. A kit comprising two or more genes derived from gene sequences which:

(a) are either homologous, or represent consensus gene sequences derived from at least three homologous genes, and

(b) carry cleavage sites, each of which:

(ba) lie at or adjacent to the ends of genetic sub-sequences which encode structural sub-elements,

(bb) are unique within each gene sequence,

(bc) do not form compatible sites with respect to any single sub-sequence, and

(bd) are common to all homologous sub-sequences.

55. A kit comprising two or more genetic sub-sequences which encode structural sub-elements, which can be assembled to form genes, and which carry cleavage sites, each of which:

(a) lie at or adjacent to the ends of said genetic sub-sequences,

(b) do not form compatible sites with respect to any single sub-sequence, and

(d) are common to all homologous sub-sequences.

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